Please amend the subject application as follows:

Amendments to the specification:

Please delete the paragraph beginning at page 25, line 11, which starts with "**Figures 23A1-23E-5.**"

Please delete the paragraph beginning at page 26, line 14, which starts with "**Figure 28.**"

Please replace paragraph beginning at page 25, line 23, with the following amended paragraph:

> **Figure 23 ~~24~~.** Exogenous IL-2 restores Th reactivity in the presence of Ts. CD4+ Th and CD8+CD28- Ts cells from the same TCL were activated alone or together with allogeneic APCs. rIL-2 (% units/ml) was added to parallel cultures at the initiation of the blastogenesis assay. CPM of triplicate reactions are shown. SD to the mean was less than 10%. The results ~~resuklts~~ represent one of three ~~thre~~ repeat experiments.

Please replace paragraph beginning at page 25, line 31, with the following amended paragraph:

> **Figure 24 ~~25~~.** Ts suppress CD40-signaling in APC. The "suppressed" APC do not upregulate the expression of costimulatory molecules (CD80, CD86) and are, therefore, unable to induce and sustain the full program of Th activity.

Please replace paragraph beginning at page 26, line 5, with the following amended paragraph:

Figure 25 ~~26~~. HLA A, B and DR values and split equivalence. Various HLA A loci, HLA B loci and HLA DR loci which may be used as antigens for priming T suppressor cells.

Please replace paragraph beginning at page 26, line 9, with the following amended paragraph:

Figures 26A-26H ~~27A-27H~~. DRB Protein Sequences. Amino acid sequences of DRB proteins correspond to hypervariable regions of HLA-DR B1 antigens. These antigens may be used as allopeptides for priming T suppressor cells.

Please replace paragraph beginning at page 26, line 22, with the following amended paragraph:

Figure 27 ~~29~~. Amino acid ~~acids~~ sequences of SLA DRA alleles. These amino acid sequences may be used for generating xenospecific human suppressor T cells in the methods described infra.

Please replace paragraph beginning at page 26, line 26, with the following amended paragraph:

Figure 28 ~~30~~. Amino acid ~~acids~~ sequences of SLA DRB alleles. These amino acid sequences may be used for generating xenospecific human suppressor T cells in the methods described infra.

Please replace paragraph beginning at page 26, line 30, with the following amended paragraph:

Figure 29 ~~31~~. Amino acid ~~acids~~ sequences of SLA DQA alleles. These amino acid sequences may be used for generating xenospecific human suppressor T cells in the methods described infra.

Please replace paragraph beginning at page 27, line 1, with the following amended paragraph:

Figure 30 ~~32~~. Amino acid ~~acids~~ sequences of SLA DQB alleles. These amino acid sequences may be used for generating xenospecific human suppressor T cells in the methods described infra.

Please replace paragraph beginning at page 27, line 6, with the following amended paragraph:

Figure 31 ~~33~~. Nucleic acid sequences encoding ILT3 protein and the amino acid sequence of the encoded ILT3. (M. Cella and M. Colonna, J. Exp. Med. 185, 1743 (1997))

Please replace paragraph beginning at page 27, line 10, with the following amended paragraph:

Figures 32A-32B ~~34A-34B~~. Nucleic acid sequences encoding ILT4 protein and the amino acid sequences of the encoded ILT4. (M. Colonna et al., J. Immuno. 160, 3096 (1998))

Please replace paragraph beginning at page 27, line 14, with the following amended paragraph:

Figure 33 ~~35~~. Proliferation of CD8+CD28+ and CD8+CD28- cells from PBMC in response to allogeneic stimulation. PBMC from donor BB1 were labeled with CFSE and stimulated in MLC with CD2-depleted PBMC from donor BB2. Cells were labeled with CD28 PE and CD8 PerCP, and analyzed by flow cytometry at day 0, 5, and 7.

Please replace paragraph beginning at page 27, line 21, with the following amended paragraph:

Figure 34 ~~36~~. Proliferation of CD8+CD28+ and CD8+CD28- cells from allogeneic TCL. Responding CD8+ T cells from TCL BB1-anti-BB2 were stimulated with CD2-depleted PBMC from donor BB2 in the presence or absence of IL-2. Aliquots of these cultures were stained at time 0, 48, and 72 hr with CD28 PE, and analyzed by flow cytometry.

Please replace paragraph beginning at page 27, line 28, with the following amended paragraph:

Figures 35A-35B ~~37A-37B~~. Suppression of alloreactivity of CD4+ T cells by CD8+CD28- T cells. Proliferative responses of CD4+ Th cells from baboon (Fig. 35A ~~37A~~) or rat (Fig. 35B ~~37B~~) T cell lines against their specific stimulators were measured in a 3-day blastogenesis assay. Irradiated CD8+CD28-

Ts cells at different Ts to Th ratios were added at the initiation of assay. The suppressive effect of Ts on Th was expressed as percent suppression.

Please replace paragraph beginning at page 30, line 7, with the following amended paragraph:

In an embodiment of the above-described method of generating antigen specific allospecific human suppressor CD8+CD28- T cells the MHC class I antigen is an HLA-A or HLA-B antigen expressed by the APC used for priming. Antigen specific suppressor ~~supressor~~ cells can be generated by T cell priming against any of the existing HLA-A or HLA-B antigens of which there are more than two hundred such antigens. One of skill may select but is not limited to the HLA-A or HLA-B antigens from the group of HLA-A and HLA-B antigens listed in Figure 25 ~~26~~.

Please replace paragraph beginning at page 30, line 18, with the following amended paragraph:

In an embodiment of the above-described method of generating antigen specific allospecific human suppressor CD8+CD28- T cells the MHC class II antigen is an HLA antigen selected from the group consisting of HLA-DR, HLA-DQ and HLA-DP. One of skill in the art will recognize that there are hundreds of HLA class II antigens. For example, HLA class II antigens may be but are not limited to DRB antigens which may be selected from but are not

limited to the group of DRB proteins listed in Figure 26 ~~27~~.

Please replace paragraph beginning at page 32, line 32, with the following amended paragraph:

In an embodiment of the above-described method of generating xenospecific human suppressor CD8+CD28- T cells, the xenogeneic mammalian antigen presenting cells (APCs) are selected from pig or primate APCs. One of skill in the art will recognize that pig antigens may be selected from numerous SLA ~~antigens~~ class I antigens. The antigens may be selected from but are not limited to the group of SLA-DRA, SLA-DRB, SLA-DRQ-A and SLA-DQB listed in Figures 27 ~~29~~ through 30 ~~32~~.

Please replace paragraph beginning at page 34, line 24, with the following amended paragraph:

In an embodiment of the above-described method of generating the antigen specific human suppressor CD8+CD28- T cells the allopeptide is a peptide antigen or a whole protein. For example, the allopeptide may be selected from an allopeptide corresponding to hypervariable regions of HLA-DR B1 antigens which may be selected from but not limited to the HLA-DR B1 antigens listed in Figure 26 ~~27~~.

Please replace paragraph beginning at page 135, line 7, with the following amended paragraph:

To explore this possibility, Ts were added to cultures containing allospecific Th and the APCs used for priming, 0, 6 and 18 h after the initiation of the assay. The expression of CD40, CD54, CD58, CD80 and CD86 on APCs was analyzed 48 h, and Th proliferation was measured 72 h, after the initiation of the cultures. In the absence of Ts, Th show strong proliferation in response to stimulation with APCs (Fig. 22) and induce the unregulation of CD54, CD58, CD80 and CD86 on APCs ~~(Fig. 23)~~. In contrast, when Ts were added to the cultures at time 0, Th proliferation was strongly inhibited (Fig. 22) and the level of CD54, CD58, CD80 and CD86 expression on APCs was greatly diminished ~~(Fig. 23)~~. The inhibitory effect of Ts decreased when they were added 6 h after initiation of cultures and was virtually absent when added 18 h later (Fig. 22~~ and Fig. 23~~). Taken together these data indicate that suppression is an early event which requires the presence of APCs and that APCs may activate $CD4^+$ Th only if they have not first interacted with Ts.

Please replace paragraph beginning at page 140, line 17, with the following amended paragraph:

There is ample evidence that in the absence of co-stimulation TCR interaction with MHC/antigen complexes can lead to T cell anergy [17-19]. T cell anergy can be restored by crosslinking the CD28 molecule ~~molecure~~ or by the use of exogenous IL-2 [17-19]. It was found that addition of rIL-2 to

cultures containing Th, Ts and APC restores Th proliferation (Fig. 23 ~~24~~). This indicates that Th are rendered anergic by Ts-treated APCs consistent with the previous finding that CD28 crosslinking restores Th reactivity in cultures with Ts [5].

Please replace paragraph beginning at page 140, line 28, with the following amended paragraph:

The data herein support a model in which T-cell mediated suppression can result from ~~form~~ the sequential interaction between first, Ts ~~TS~~ and APCs and next, "suppressed" APCs and Th (Fig. 24 ~~25~~). In this regard, the present findings confirm and extend the "temporal bridging" model recently described to account for the complex role that APCs play in Th-mediated generation of CD8+ Tc [2-4]. Furthermore, the present data complement the finding that CD40 signaling is essential for conditioning APCs, by demonstrating that Ts inhibit this pathway. New data show that Ts inhibit Th-induced ~~The-induced~~ activation of NF-B in APC, thus interfering with the upregulation of B7 costimulatory molecule (Li, J., Liu, Z., Jiang, S., Cortesini, R., Lederman, S., Suciu-Foca, N. submitted).

Please replace paragraph beginning at page 148, line 11, with the following amended paragraph:

ILT3 (1) and ILT4 (2) the amino acid sequences of which and the nucleic acid sequences encoding these proteins are set forth in Figures 31A-31B ~~33A-33B~~

and 32 ~~34~~, respectively, belong to a family of leukocyte inhibitory receptor (LIRs) which bear homology to killer inhibitory receptors (KIRs). These molecules interact with either MHC-Class I-like proteins or other unknown ligands and recruit an inhibitory signaling protein, ShP-1.

Please replace paragraph beginning at page 162, line 16, with the following amended paragraph:

To determine whether CD8+CD28- T cells from freshly isolated PBMC are able to proliferate in response to allogeneic APC, PBMC from donor BB1 were labeled with the vital dye CFSE and stimulated in MLC with CD2-depleted PBMC from donor BB2. Aliquots of this culture were stained on day 0, 5, and 7 with mAb CD28 PE and CD8 PerCP, and analyzed by flow cytometry. CD28 expression and simultaneous loss of the vital dye CFSE were measured within the CD8 gated (G1) population. As indicated in Fig. 33 ~~35~~, all CD8+ cells were positive for CFSE on day 0. However, on day 5, 16.6% of the CD8+ T cells proliferated in response to allogeneic stimulation, showing loss of CFSE (% upper left quadrant + % lower left quadrant). Among the proliferating cells, CD8+CD28- cells represented only 2.9% of the total CD8+ cells (lower left quadrant), while CD8+CD28+ T cells accounted for approximately 13.7% of the CD8+ cells (upper left quadrant). By day 7, the percent of total CD8+ cells which had divided increased to 42.7%. Among these cells, CD8+CD28- cells represented 4.4% of the total CD8+ cells (lower left

quadrant), while CD8+CD28+ T cells accounted for 38.3% (upper left quadrant). Interestingly, 57% of the CD8+ cells found alive in the culture on day 7 did not proliferate and did not undergo any morphological changes indicative of apoptosis. Also, they did not acquire annexin V expression (data not shown). The failure of a significant proportion of CD8+ T cells to be recruited in the dividing pool may reflect distinct activation requirements of different T cell populations (e.g., different TCR or naive versus memory T cells).

Please replace paragraph beginning at page 163, line 14, with the following amended paragraph:

In the next series of experiments studied was the proliferation capacity of stimulated (memory) CD8+CD28- T cells isolated from allogeneic TCLs. TCL BB1-anti-BB2 was generated by two rounds of stimulation of PBMC from individual BB1 with irradiated PBMC from donor BB2. T cells from TCL BB1-anti-BB2 were collected on day 14, subjected to depletion of CD4+ cells, and labeled with CFSE. Cells were then challenged with CD2-depleted APC from donor BB2 in the presence or absence of IL-2, and stained with mAb CD28. Flow cytometry analysis indicated that CD8+ cells did not proliferate after 48 or 72 hr of culture in the presence of APC alone, but proliferated when challenged with APC and IL-2 (Fig. 34 ~~36~~). Proliferating CD8+CD28+ represented 19.0% and 31.0% of the total CD8+ T cells at 48 and 72 hours, respectively. Proliferating CD8+CD28-

cells accounted for 9.2% and 52.8% of all CD8+ T cells at 48 and 72 hr, respectively. These results indicate that in contrast to the previously described senescent CD8+CD28- T cells, a significant fraction of the CD8+CD28- subset does have proliferative capacity. Our data are ~~is~~ reminiscent of the finding that human CD8+CD28- T suppressor cells primed in vitro by multiple stimulation with allo- or xenogeneic APC display an oligoclonal TCR VB gene expression (6), indicating preferential expansion of a skewed T cell repertoire. The results here also suggest that CD8+CD28- Ts, that downregulate the immune response, have at first a low proliferating rate, but reach a sizable population upon repeated stimulation with antigen.

Please replace paragraph beginning at page 169, line 18, with the following amended paragraph:

To investigate the generality of Ts mediated suppression that we observed in humans, explored was the possibility of generating allospecific Ts in baboon and rat. After two stimulations in vitro with allogeneic PBMC, there is a population of CD28- T cells in CD8+ subset in baboon T cell line. This population of T cells suppressed the proliferative response of CD4+ T cells from the same T cell line to allogeneic APC in a dose-dependent manner (Fig. 35A ~~37A~~). Similarly, rat spleen cells primed in vivo contained a very small population of CD8+CD28- T cells. Dose-dependent suppression was also

revealed when those cells were added to Th and APC mixture (Fig. 35B ~~37B~~).

Amendments to the Drawings:

Please replace Figures 1 through 37 with the replacement sheets for these Figures annexed hereto as **Exhibit A.**